Antiidiotype induction therapy: evidence for the induction of immune response through the idiotype network in patients with ovarian cancer after administration of anti-CA125 murine monoclonal antibody B43.13.

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The immune status of ovarian cancer patients receiving anti-CA125 murine monoclonal antibody B43.13 was evaluated by measuring antiidiotypic antibodies (Ab2), antiantiidiotypic antibodies (Ab3), antiisotypic human antimouse antibodies (HAMA), interferon-gamma, and CA125 levels in the serum. A specific assay was developed for the determination of Ab2 antibodies using chimeric MAb B43.13. Of the 50 patients studied, 26 had elevated levels of Ab2. Eleven of these 26 patients also had high titer of antiantiidiotypic (Ab3) antibodies. Eight of the 22 patients analyzed had increased interferon-gamma levels. A tentative correlation was found between survival of these patients' antiidiotype induction.

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A monoclonal antiidiotypic antibody ACA 125 mimicking the tumor-associated antigen CA 125 for immunotherapy of ovarian cancer.

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A new concept of oncological immunotherapy comprises the attempt to trigger the immune system of the host into a response against tumor cells. Antiidiotypic antibodies bearing the internal image of an antigen expressed on the surface of the tumor seem to be most suited for this purpose. We have generated a murine antiidiotypic antibody (ACA 125) functionally imitating the tumor-associated antigen CA 125, which can be detected in about 80% of ovarian carcinomas. The hybridoma cell was adapted to serum-free medium and antibody was produced in a hollow fiber cell culture system (Technomouse). ACA 125 (Ab2) shows high affinity for the paratope of Ab1 (affinity constant: 2.3 x 10(9) liters/mol) and binding of Ab2 to Ab1 is completely inhibited by the nominal antigen. Application of F(ab')2 fragments of ACA 125 to rats lead to an anti-CA 125 immunity by production of IgG and IgM antiantiidiotypic antibodies (Ab3) that bind to both ACA 125 and CA 125. Furthermore the induction of a non-MHC-restricted cell-mediated cytotoxicity for human ovarian adenocarcinoma cell line NIH-OVCAR3 (expressing CA 125 on its surface) could be proved; additionally complement-dependent cytotoxicity (CDC) as well as an antibody-dependent cellular cytotoxicity (ADCC) was observed. Thus, monoclonal antiidiotypic antibody ACA 125 fulfills recent criteria for an antibody, which might be successful in immunotherapy using the anti-idiotypic network approach.

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Activating anti-idiotypic human anti-mouse antibodies for immunotherapy of ovarian carcinoma.

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Human anti-mouse antibodies (HAMA) are observed frequently after immunoscintigraphy with monoclonal antibodies (MoAb) directed against CA-125. As the authors have shown previously, HAMA can cause false-positive CA-125 values in routine CA-125 immunoradiometric assay (IRMA) tumor-marker assays (in one case, up to 900 days after immunoscintigraphy). In 32 patients, the authors found a HAMA frequency of 34% (11/32: 3/7 after the first administration, 6/13 after the second, and 2/2 after the third). Ten patients developed extremely high CA-125 levels after undergoing the CIS IRMA assay (up to 80,000 U/ml) in parallel to a significant HAMA increase. The use of different assays, or HAMA removal before in vitro testing, can solve this problem. After a new CA-125 assay containing antibodies that recognize different epitopes on the CA-125 antigen (Biomira Tru-Quant OV) was applied, only mildly increased assay results or normal levels were measured. Most of HAMA-positive patients demonstrated a predominantly anti-idiotypic response, determined with two different HAMA assays. Seven patients with anti-idiotypic HAMA responses after OC-125 immunoscintigraphy remained free of tumor or had stable disease (2-42 or more months), contrary to their poor prognoses that had been made based on the underlying stages of their tumors. All of these patients are currently doing well (Karnofsky Index > 70%) and show no significant tumor progression. In light of their extremely poor prognoses (5-year survival rates of 3-5% in recurrent International Federation of Gynecology and Obstetrics III/IV stages), without further chemotherapy, these courses are extremely unusual. Preliminary in vitro experiments lead to the postulation that anti-idiotypic HAMA may trigger an antitumor effect either by suppressing the growth of CA-125-expressing cancer cells directly, or by activating the patient's immune response via induction of Ab3. Similar results are observed after immunoscintigraphy with a technetium-99m-labeled anti-CA-125 monoclonal antibody (B43.13), which the authors now also use for immunotherapy of ovarian cancer patients by repeated

Clinical evaluation of a new two-site assay for CA125 antigen.

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As appropriate surgery and chemotherapy can improve both quality of life and survival of patients with ovarian adenocarcinoma, there has been a pressing need for "serodiagnostic" assays to enable close patient monitoring. CA 125 antigen has previously been described as a useful tumor marker of ovarian cancer. This is the first clinical evaluation of a radioimmunoassay using two new monoclonal antibodies, B27.1 and B43.13, that react with separate sites on the glycoprotein marker CA 125. Using the new assay, the majority of patients with clinically or radiologically detectable disease had serum CA 125 antigen levels well above the upper limit seen with random apparently healthy donors, while only three patients who were believed free of disease had elevated levels. Disease progression was associated with increasing values of serum CA 125 antigen, while response to therapy was associated with a steady decline in serum CA 125 antigen levels. Seven patients had steadily rising serum CA 125 antigen levels after initially having normal levels. The mean lead time between rise above normal and clinical or radiological evidence of relapse was 5 months (range 2 to 12 months). The merits of further surgical intervention are illustrated by the serial values of two patients followed after chemotherapy. The assay appears to have value in monitoring response to therapy and in detecting disease relapse at a time when appropriate therapeutic intervention is still possible or likely to be beneficial. Furthermore, monitoring CA 125 antigen was shown to be of benefit in assessing response to chemotherapy in a few patients with metastatic adenocarcinoma of unknown primary, and may be useful in this group of patients in determining those likely to benefit from aggressive chemotherapy.

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Evidence for interaction of human anti-idiotypic antibodies with CA 125 determination in a patient after radioimmunodetection.

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Very high concentrations of CA 125 have been found in some ovarian cancer patients after repeated radioimmunodetection with anti-CA 125 antibodies [OC125-F(ab')2]. In one patient we measured a CA 125 concentration of 135,000 kilo-arb. units/L, using an enzyme immunoassay involving OC125 antibodies. With an immunoradiometric assay involving use of two new anti-CA 125 antibodies (B43.13 and B27.1), the CA 125 concentration was 34 kilo-arb. units/L, indicating a discrepancy. The component responsible for the high result in the enzyme immunoassay could be purified by immunoaffinity chromatography on Protein A-Sepharose. Furthermore this component bound to anti-human IgG-Sepharose in the same manner as did the serum IgG fraction. Adsorption of human anti-mouse antibodies present in the serum did not decrease the CA-125-like material. Binding of whole OC125 antibodies to the purified CA-125-like material was inhibited completely in the presence of CA 125 antigen. We infer that the false-positive CA 125 activity is ascribable to a human IgG directed against an idiotope of the OC125 antibody, which was induced by repeated application of OC125 antibodies. To avoid falsely positive results in patients receiving OC125 antibodies, CA 125 should be measured by an assay in which other antibodies are used.

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